# Editorials

## On Violating Promises

SOME MONTHS AGO *American Medical News* reprinted an article by Harry Schwartz that had been published by *The New York Times*. It pointed out that, of all Americans, doctors who treat Medicare patients are the only ones legally compelled not to raise their fees. It was his opinion that doctors are getting a raw deal, and surely there is support for this opinion among physicians. He went on to point out that the mandated freeze on these physicians' fees violated "openly and plainly" the promise made to physicians when the Medicare law was passed in 1966, and speculated on what might happen if government promises made to other citizens were also to be violated. He notes that "when government openly and enthusiastically violates its promises to one important group of Americans—doctors—the precedent has been set for violating promises to others" and asks "if breaking promises to doctors is all right, then what's wrong with breaking promises to 'rich' people who own government securities," for example.

These are times when what happens in health care may be a bellwether for what could happen elsewhere in our society. As Schwartz points out, government has made many promises to many people over the years, and when these are not kept, for whatever reason, trust in government and therefore in the American system becomes eroded, with eventual economic and political consequences no one really wants to think about. Schwartz's point could prove to be an important one, or so it seems to this writer.

MSMW

## Navigating the Sea of Eicosanoids

"PROSTAGLANDINS, THROMBOXANES AND LEUKOTRIENES in Clinical Medicine" by Zipser and Laffi introduces the fundamental concepts critical to an understanding of the structural diversity and functional complexity of eicosanoid metabolites of arachidonic acid. Many of the metabolites generated by the enzymatic actions of cyclooxygenases and lipoxygenases on arachidonic acid are potent mediators of cellular and organ system responses that have potentially important roles in physiologic processes and disease states. The combined effects of multiple eicosanoid mediators that differ in action and potency often determine the overall biological response. A further element of adaptability is provided by the varied mechanisms of recognition and regulation of the mediators by target cells.

Generation and biodegradation of some products of the oxygenation of arachidonic acid involve one or more cell-cell interactions. For example, some 15-lipoxygenase products from eosinophils, epithelial cells and endothelial cells stimulate 5-lipoxygenase activity in mast cells and inhibit that expressed in macrophages and neutrophils.[1,2] The 5-hydroxy-eicosatetraenoic acid (5-HETE) released by neutrophils, macrophages or mast cells may be converted to double oxygenation products by 15-lipoxygenases of eosinophils or 12-lipoxygenases of platelets in mixed cell populations.[3] Cellular cooperativity not only leads to the production of novel dihydroxy and trihydroxy eicosanoid mediators with distinct activities, but also enhances the generation of mediators by any one type of cell through stimulatory factors released by another cell. In addition, some cells appear to degrade eicosanoid mediators released by other cells engaged in active synthesis. C-6 peptide leukotrienes synthesized by macrophages or mast cells are inactivated by halide-dependent peroxidases released from eosinophils.[4] Knowledge of these concerted synthetic mechanisms and pathways of degradation is critical to the interpretation of data from in vitro studies of isolated cells in relation to their significance in vivo.

A separate set of stereospecific receptors on target cells transduces the effect of each eicosanoid mediator.[5-7] Some target cells express subsets of receptors for a single mediator that transduce different functional responses. For example, human neutrophils have a high-affinity subset of receptors for leukotriene (LT) $B_4$ that are coupled to activation of chemotaxis and increased adherence and a low-affinity subset that elicits release of lysosomal enzymes and enhanced oxidative metabolism.[8] Thus, two concentrations of an eicosanoid mediator may interact with even one type of cell through different receptors with qualitatively distinct consequences. The choice of a pharmacologic antagonist may require estimation of the expected concentrations of such mediators for optimally specific competition at the receptor level.

The presence of different eicosanoid receptors that transduce specific effects suggests the possibility of finding biologically opposite effects of two eicosanoid mediators generated by the same pathway in one tissue. Thromboxane (Tx) $A_2$ and prostaglandin (PG) $I_2$ are generated when platelets adhere to damaged vascular endothelium. $TxA_2$ stimulates vasoconstriction and platelet aggregation, whereas $PGI_2$ promotes vasodilation and inhibits platelet aggregation. Thus it may be difficult to predict the results of inhibition of the shared pathway that produces $TxA_2$ and $PGI_2$ unless differences exist in the susceptibility to inhibition of activity of later synthetic steps. Opposite actions of a single mediator are sometimes identified in different types of target cells. For instance, $LTB_4$ stimulates the functions of T-suppressor cells and inhibits those of T-helper cells in vitro.[9] In other organ systems, the effects of eicosanoid mediators are additive or synergistic.

Some eicosanoid mediators act as second messengers for the primary actions of other eicosanoids. $LTB_4$ acts principally to augment the leukocytic components of inflammation. It also evokes bronchospasm, although with far lower potency than $LTC_4$ or $LTD_4$. The mechanism of transduction of the weaker effects of $LTB_4$ involves stimulation of the cyclooxygenation of arachidonic acid by target tissues, which leads to local generation of the potent bronchoconstrictor $TxA_2$. Inhibitors of cyclooxygenation thus may suppress the effects of 5-lipoxygenase-derived mediators.[10-12] In some instances, eicosanoids may condition the responses of tissues to other